Remarks and Arguments

Claims 21-28 are pending in this case. Claims 22 and 23 have been withdrawn because the Office believes they are drawn to non-elected subject matter.

35 U.S.C. § 112

1. Written description

Claim 28 stands rejected as allegedly failing to comply with the written description requirement. According to the Office, the phrase "wherein the first set of conditions comprises culturing the cells in the presence of matrix without a feeder layer," is new matter. Applicants traverse the rejection.

Applicants note that culturing the cells in the presence of matrix without a feeder layer is supported by the specification (page 7, lines 25-29). Withdrawal of the rejection is respectfully requested.

2. Enablement

Claims 21 and 24-28 stand rejected under 35 U.S.C. § 112 as allegedly not enabled. The Office admits that the specification discloses high levels of expression of PODXL in undifferentiated hES cells and decreased levels of PODXL expression after growing the hES cells in unconditioned culture media, where PODXL expression level is measured by real time PCR. The Office alleges that the specification fails to provide adequate guidance for how to measure the presence of undifferentiated hES cells by measuring PODXL protein expression level. According to the Office it was known in the art that cDNA or mRNA levels do not necessarily correspond to protein level expression. Applicants traverse the rejection.

Applicants have concurrently submitted an information disclosure statement citing Economou et al. (2004) *Journal of Cell Science* 117:3281 ("Economou"), which compares expression levels of human PODXL as measured by mRNA and protein expression under various conditions. In particular, the Office is urged to consider Figures 1 and 2 in Economou. Figure 1 examines PDXL protein expression level when human glomerular epithelial cells (HEGC) are grown on different substrates. Graphs D-F quantify protein expression levels.

Notably graph E indicates the highest level of PDXL protein expression was achieved when the cells were cultured on 20 ug/cm^3 of laminin. While the other two substrates (GBM and

collagen) did not show a dose response effect, GBM was clearly better than collagen (Graphs D and E). In the results presented in Figure 2 mRNA levels of PDXL were examined. The mRNA expression results correlate well with the protein expression level results. Thus HEGC grown on laminin at 20 ug/cm^3 produced the highest level of PDXL mRNA expression (Figure 2B). HEGC grown on collagen at 20 ug/cm^3 produced the lowest level of PDXL mRNA expression and HEGC grown on GBM at 20 ug/cm^3 resulted in an intermediate level of PDXL mRNA expression (Figure 2B). In short, protein expression levels of human PDXL correlated well with mRNA expressions of human PDXL. Applicants submit that these data address the Office's concerns regarding potential disparities between PDXL mRNA expression levels and corresponding protein expression levels.

In our previous response Applicants argued that Hara et al., (made of record previously in this case) demonstrated that mRNA levels of the murine homolog of PDXL correlated well with protein expression. The Office dismissed Applicants arguments stating "mouse and human genes are different genes and they encode different proteins," (Office Action dated10/12/07, page 6). However, now the Office relies on Spence et al., (2006) *Molecular Cancer Research* 4(1):47, alleging this reference demonstrates mRNA levels do not correspond to protein expression levels. Quoting from Spence, the Office states, "In the majority of publications, **total** mRNA is analyzed, which does not reflect the level of translation of **a given** transcript. However, experiments **in yeast** indicate that there is little correlation between mRNA abundance and protein level," (Office Action dated 10/12/07, page 4)(emphasis added). Applicants are confused as to how the Office can summarily dismiss a reference Applicants cite regarding murine PDXL levels, yet at the same time base its rejection on a quote from Spence, which: 1) is specific to yeast; and 2) is a generalization about all yeast proteins (stating nothing about a homolog of PDXL). The Office seems to suggest that a yeast model provides a better model for human systems than a murine model. Applicants disagree.

Turning next to the first sentence quoted from Spence, Applicants note that this merely indicates that total cellular mRNA has no correlation to the expression level of a specific protein. Applicants believe this has no relevance to the question at hand which is does mRNA expression levels of PDXL correlate with protein expression levels of PDXL. Applicants have made of record two references that state that it does and thus submit the claims are enabled.

The Office also suggests that the claims read on a "tissue or organ culture" and states that there is no evidence of record to indicate PDXL expression levels would change in this type of culture. Applicants note that there is evidence of record that suggests PDXL levels will change as long as undifferentiated hES cells are differentiating. If the Office questions the enablement of Applicants' invention it is reminded of its burden in this regard:

> It is incumbent upon the Patent Office, whenever a rejection on this basis [enablement] is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure **and to back up its assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement.** *In re Marzocchi* 169 U.S.P.Q. 367, 369 (CCPA 1971)(emphasis added).

To date, no reasoning why an "organ culture" would differ from any other culture comprising hES cells has been presented and no evidence supporting that reasoning has been made of record.

Finally Applicants remind the Office that working examples of every embodiment of the invention are not required to satisfy the enablement requirement.

> To the extent the examiner believes that the specification must 'teach how to make and use all bispecific . . . antibody[ies] . . . where one arm is specific for *all* target tissue of the patient and the other arm is specific for all undisclosed F-18 labeled peptide[s]' . . . we note that no authority has been cited in support of this requirement. To the contrary, appellants are *not* required to disclose *every* species encompassed by their claims even in an unpredictable art. *Ex parte Griffiths* BPAI Appeal No. 2004-1660 at page 4 (citing *In re Angstadt*, 190 USPQ 214, 218 (CCPA 19676)(emphasis in the original)

For all of the reasons set forth above, Applicants believe the claims are enabled. Withdrawal of the rejection is requested.

CONCLUSION

In view of the foregoing remarks, Applicants respectfully request the reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this filing and charge any additional required fees to our deposit account No. 07-1139 referencing the docket number indicated above.

Respectfully submitted,

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